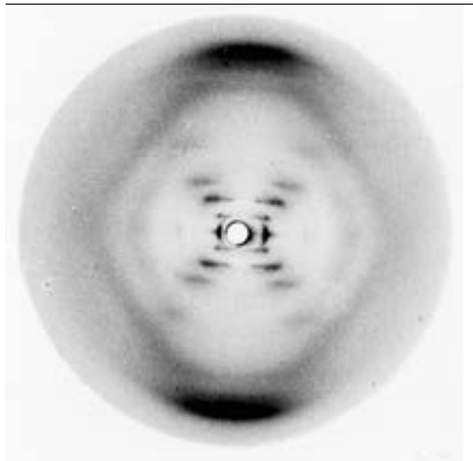


DISCOVERING THE DOUBLE HELIX

A look back in time to the history of the discovery of DNA and its structure – work which would change medicine and science forever.

DNA is as old as history itself, but human understanding of the genetic code that determines the shape, size, colour and behaviour of all living things only began its embryonic formation in 1859 with the publication of Charles Darwin's trailblazing work *On The Origins of Species by Means of Natural Selection*. Though the book offered nothing in the way of a biochemical explanation for its theories, its suggestion that life hadn't magically appeared but had copied itself, adapted and evolved over time – vast time – changed the focus of scientific imagination and enquiry.

Gregor Mendel, a monk and teacher with a sideline in science and research, living in what would be the modern-day Czech Republic, took the next step. Between 1856 and 1863 he conducted thousands of cross-breeding experiments on pea plants. He observed not just the characteristics that passed from one generation to the next but also the ratios of those inherited characteristics. The paper that came out of this intensive observation, *Experiments on Plant Hybridisation*, published in 1866, was so far ahead of its time that it wasn't until 1900 that other scientists had caught up with him and rediscovered his work. Only then could they appreciate the thoroughness of his methodology and understand the implications of what he had found – that

Left. Photo 51 – an X-ray diffraction image of DNA.
Right. Rosalind Franklin.

IMAGES: KINGS COLLEGE LONDON/ALAMY

Left. The Nobel winners 1962. Photo shows left to right they are Professor Maurice Wilkins, Dr Max Perutz, Dr Francis Crick, John Steinbeck, Professor James Watson and Dr John C Kendrew.
Right. Francis Crick's original sketch of the structure of DNA made in 1953.

each parent possesses a specific pair of "somethings" and passes one of these "somethings" on to its offspring so that it too now possesses a pair. He had, in effect, mapped out genetic science.

Extraordinary discovery

More was to come, this time from Germany. There, in 1869, the Swiss chemist Friedrich Miescher, asked a local surgery to send him all its used bandages – the pus that filled them being a rich source of the white blood cells he wanted to investigate. He isolated the cells and identified their various proteins, but also he found another substance in the cell nuclei that bore no resemblance to the other proteins and had an unusual chemical makeup. Meischer knew he had found something extraordinary, and though he couldn't say exactly what it was, he suspected it was linked to chemical inheritance. He called his discovery "nuclein", which later become "nucleic acid" and finally morphed into "deoxyribonucleic acid" – DNA. Again, though, it would be several decades before the rest of the scientific community grasped the significance of what he had done.

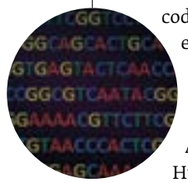
From 1905 onwards, the Lithuanian-born biochemist Phoebus Levene, working at the Rockefeller Institute of Medical Research in New York, was examining nucleic acid in the sort of detail that Miescher could not have dreamt of just 35 years' earlier. Levene found two types of nucleic acid, DNA and RNA (ribonucleic acid), and, more importantly, the components of DNA: adenine (A), guanine (G), thymine (T), cytosine (C) and deoxyribose phosphate. He also detected the phosphate-sugar-base order of the components, which sorted them into units that he named nucleotides. Levene didn't get it all right, though: he described the wrong structure for DNA and believed that its chemical makeup was far too simple to carry any genetic code – a belief that would persist for some time.

At the same time that Levene was working in his laboratory, the theories of evolution and genetic inheritance were being seized upon by the eugenics movement. This made several fundamental misinterpretations of the basic science, then applied them to the goals of social and population control. The movement found expression in sterilisation programmes in several countries, became more overtly political as the underpinning for the US Immigration Act of 1924 and was a driving force behind the theory of racial superiority in Nazi Germany, which grew to horrific proportions with the systematic destruction of the Jews and other "inferior" and "undesirable" people.

Transforming principle

By 1944, with the end of World War Two in sight, the real science was making further progress. Also at the Rockefeller Institute in New York, the Canadian bacteriologist Oswald Avery was busy following up the work from the late 1920s of the British microbiologist Frederick Griffith, who had found that a severe form of pneumonia could, in some way, activate a non-virulent form. Avery and his colleagues, Colin MacLeod and Maclyn McCarthy, went looking for this "transforming principle", and systematically began to isolate the factors that could have caused one type of pneumonia cell to change into another. The belief among the wider scientific community was that a protein had to be responsible, but after eliminating all the possible proteins and carbohydrates the Avery team had shown that nucleic acid, DNA, held the key – their results suggested that it alone was the carrier of hereditary material.

The paper they published in the *Journal of Experimental Medicine* in February 1944 divided opinion. Some biochemists still clung to the belief that the A,G,C,T of DNA was too simple and limited to carry the huge complexity of biological material required. But a few other experts reasoned that since DNA was present in every chromosome it might just as well be the means of transporting genetic coding, even for more complex entities, such as human beings.



A new language

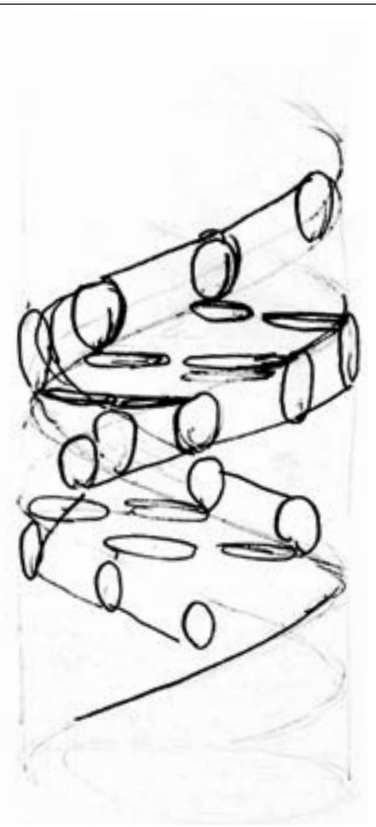
Among the champions of Avery's work was the Austro-Hungarian biochemist Erwin Chargaff, who had fled the Nazis and found a position at Columbia University in New York. "Avery gave us the first text of a new language, or rather he showed us where to look for it," wrote Chargaff. "I resolved where to search for this text." He began to look more closely at the composition of DNA in bacteria and larger organisms.

Also in 1944, the Austrian quantum physicist Erwin Schrödinger, he of the famous cat, and yet another leading thinker who escaped the Nazi regime, published a short book called *What is Life?* In this he suggested that life centred around a complex molecule that stored genetic material and passed it on to future generations. He also proposed that this biological information might resemble the dots and dashes of morse code.

One of the people who read *What is Life?* was James Watson, then a startlingly young student at the University of Chicago. "Schrödinger struck a chord because I too was intrigued by the essence of life," Watson wrote. "The notion that life might be perpetuated by means of an instruction book inscribed in a secret code appealed to me." Schrödinger's book also caught the imagination of the British physicist-turned-chemist James Crick, who had been working in the Admiralty Research Laboratory throughout the war, and whose thoughts now turned to biology.

Focusing efforts

In 1951, at the age of 35, Crick was working on his PhD in the Medical Research Council (MRC) unit at Cambridge University when he found himself sharing lab space with a new arrival from the US – the 23-year-old Watson, who had come to Cambridge in order to master X-ray diffraction, which, he hoped, would help him unlock the secrets of DNA. The pair soon became friends and focused their efforts on DNA. Crick also introduced Watson to Maurice Wilkins, a biochemist from New Zealand who worked at King's College in London, had extensive experience of X-ray diffraction, and even suggested the structure of DNA might be a helix.



IMAGES: ALAMY/SHUTTERSTOCK

One of Wilkins' colleagues at King's was Rosalind Franklin, who had graduated in chemistry from Cambridge in 1938 and gone to Paris after the war to learn X-ray diffraction. She returned to London in 1951 to take up a fellowship in King's MRC unit and set to work on producing diffraction images of DNA, though the head of the unit had failed to inform Wilkins of this. With the help of Raymond Gosling, a PhD assistant, Franklin captured several X-ray images of DNA, including the now-famous Photo 51. The forthright Franklin and the understated Wilkins found it hard to work together, so it fell to Crick and Watson to put the pieces together.

In early 1953 they began constructing a molecular model of DNA, drawing on the work of the team at King's College, and in particular the B version of Photo 51, which showed evidence of the helix structure.

"[Crick] realised right away that it would result in the two strands of the double helix running in opposite directions..."

It's claimed that Wilkins had given Crick and Watson the photo without Franklin's knowledge. Crick and Watson also took what they needed from the findings of Erwin Chargaff on the base-pair ratios, and from the theoretical work of Linus Pauling at the California Institute of Technology, who was also attempting to construct his own model of DNA.

Simple and elegant

Watson writes that on the morning of 28 February 1953 "the key features of the DNA model fell into place. The two chains were held together by strong hydrogen bonds between adenine-thymine and guanine-cytosine base pairs... [Crick] realised right away that it would result in the two strands of the double helix running in opposite directions... It was quite a moment. We felt sure that this was it. Anything that simple, that elegant just had to be right."

Just a few weeks later in April, they published their findings in *Nature*. The structure of DNA had been revealed – the famous double helix – and the path of biochemistry had been set on a new course. The 1962 Nobel Prize in Physiology or Medicine went to Crick, Watson and Wilkins. Franklin's name was absent: she had died in 1958 from ovarian cancer, a disease that has hereditary traits. At that time the structure of the model had not been verified: though it was to follow shortly, Nobel rules prohibited posthumous nominations. BMS